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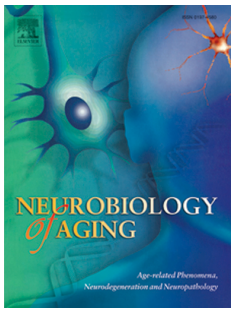

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DELINEATING THE TOPOGRAPHY OF AMYLOID-ASSOCIATED CORTICAL ATROPHY IN DOWN'S SYNDROME

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ABSTRACT

OBJECTIVE: Older adults with Down Syndrome (DS) often have Alzheimer's disease (AD) neuropathologies. While PET imaging studies of amyloid deposition (Aβ) have been associated with worse clinical prognosis and cognitive impairment, their relationships with cortical thickness remain unclear in people with DS.

METHODS: In a sample of 44 DS adults who underwent cognitive assessments, [^{11}C]-PiB PET and T1-MPRAGE, we used mixed effect models to evaluate the spatial relationships between Aβ binding with patterns of cortical thickness. Partial Spearman correlations were used to delineate the topography of local Aβ-associated cortical thinning.

RESULTS: [^{11}C]-PiB BP_{ND} was negatively associated with decreased cortical thickness. Locally, regional [^{11}C]-PiB retention was negatively correlated with cortical thickness in widespread cortices, predominantly in temporo-parietal regions.

CONCLUSION: Contrary to the prevailing evidence in established AD, we propose that our findings implicate Aβ in spatial patterns of atrophy that recapitulated the "cortical signature" of neurodegeneration in AD, conferring support to recent recommendations for earlier disease-interventions.

INTRODUCTION

Down's Syndrome (DS) is the most common neurodevelopmental disorder caused by the presence of trisomy 21 (1:800 live births). The extra copy of chromosome 21 is associated with a 4-5 fold overexpression of the amyloid precursor protein (APP) gene and increased accumulation of cerebral beta-amyloid (Aβ) deposition (Wiseman et al., 2015). The "amyloid cascade hypothesis" – the most widely accepted biomarker model of disease progression in AD – postulates that amyloidosis is the initiating event in the pathogenesis of dementia, triggering a self-perpetuating cascade involving tau hyperphosphorylation, synaptic injury, downstream macroscopic brain atrophy, and ultimately clinical decline (Hardy, 2002).

Convergent lines of evidence support a similar Aβ-induced pathogenic cascade in people with DS (Neale et al., 2018). Histopathological studies have observed a high prevalence of neuritic plaques and neurofibrillary tau tangles (NFTs), occurring as early as the 20s and in nearly all DS adults after the age of 40. The clinical and imaging phenotypes of DS also appear to show a similar spatiotemporal evolution to that seen in sporadic AD; people with DS develop cognitive decline in adulthood (Hithersay et al., 2017) and show patterns of brain atrophy especially in the hippocampal regions and temporo-parietal cortices (Annus et al., 2017; Dickerson et al., 2009; Mullins et al., 2013; Teipel et al., 2004). This temporo-parietal atrophy in DS adults emerges in the presence of

cerebral amyloidosis as measured by elevated [^{11}C]-PiB binding (Annus et al., 2017). Such a pattern of atrophy is also similar to previous studies in AD, wherein cortical thinning has been proposed as a sensitive surrogate of disease progression and neurodegenerative changes in AD (Dickerson et al., 2009).

Precisely how Aβ accumulation might lead to neurodegeneration, however, remains uncertain. Studies in the AD and cognitive impaired cohorts suggest that Aβ accumulation reaches an early plateau whereas atrophy is progressive (Jack et al., 2013), in turn meaning that the two phenomena are not correlated (Josephs et al., 2008). An advantage of studying DS, in contrast, is that the inevitability of Aβ accumulation means that one can study the influence of Aβ deposition to atrophy before cognitive decline has begun and with a range of severities of both phenomena. To this end, cortical thickness has been proposed and recognized as a sensitive surrogate of neurodegeneration AD (Dickerson et al., 2009).

To explore the pathological associations of Aβ and cortical thickness in DS, we performed a multi-modal imaging study involving [^{11}C]-PiB imaging and structural MRI, and examined the extent to which regional Aβ maps onto cortical thickness in a DS cohort at various stages of amyloidosis (i.e. presence or absence of substantial Aβ burden) and

cognitive functioning (i.e. no evidence of acquired cognitive impairment versus age-related acquired cognitively impaired or demented). Our primary hypotheses were as follows: (a) increased Aβ is associated with decreased cortical thickness, and (b) this relationship would be stronger before the onset of objective cognitive decline.

METHODS

Study design and participants

Forty-four participants with DS aged 25 – 65 volunteered to take part and successfully completed the neuropsychological assessments and imaging protocol of this study. Participants were identified via services for people with intellectual disabilities in England and Scotland, through the Down's Syndrome Association or following responses to our website. All participants had previously received a clinical diagnosis of DS based on having the characteristic phenotype. The study was approved by the National Research Ethics Committee of East of England and the Administration of Radioactive Substances Advisory Committee. Written consent was obtained from all adults with DS with the capacity to consent. For participants lacking the capacity to consent, the procedures set out in the England and Wales Mental Capacity Act (2005) or the Adults with incapacity (Scotland Act), depending on place of residence, were followed.

Clinical assessments

All participants were assessed for dementia using the Cambridge Examination for Mental Disorders of Older people with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS) informant interview, designed for diagnosing dementia in this population (Roth et al., 1986). An experienced clinician (S.H.Z. or A.J.H.), who was blinded to the age of the participant and the PiB status, allocated each participant into the categories of **(a)** those without acquired cognitive impairment, **(b)** cognitive decline, **(c)** or dementia. Dementia was diagnosed in accordance with the International Classification of Diseases-10 (ICD-10) criteria for dementia. The diagnosis of "cognitive decline" was given to participants with informant reported evidence of functional decline in one or more cognitive domains without fulfilling the full ICD-10 criteria for dementia.

Imaging protocol

Structural MRI

The T1-MPRAGE data were processed using Freesurfer (v5.3, available from https://surfer.nmr.mgh.harvard.edu) to estimate cortical thickness in 34 ROIs per hemisphere, based on the Desikan-Killiany parcellation scheme (Desikan et al., 2006). The technical procedures for surface reconstruction and quantification of cortical thickness have been described previously (Fischl and Dale, 2000). Briefly, the process involved automated non-uniformity bias correction, skull stripping, segmentation of the white matter and the boundary between the white and grey

matter. Segmented and skull-stripped data of all partic- ipants were visually inspected for parcelation errors, and topolog- ical defects in the gray/white matter boundary were manually corrected. The gray/white boundary served as a starting point for a deformable surface algorithm to compute the gray/white and pial surfaces, from which cortical thickness is calculated as the closest distance from the gray/white matter boundary to the pial surface at each vertex on the tessellated surface. In addition, PetSurfer was used to segment additional regions, such as the cerebral CSF, pons, skull and air cavities to facilitate partial volume correction of PET data (Greve et al., 2014).

[^{11}C]-PiB PET imaging

[^{11}C]-PiB data were acquired in three-dimensional (3D) mode on a GE Advance scanner. Before [^{11}C]-PiB injection, a 15-minute transmission scan using rotating ^{68}Ge rod sources was acquired to correct for photon attenuation. [^{11}C]-PiB was produced with high radiochemical purity (>95%) and specific activity (>150 GBq/umol). [^{11}C]-PiB was injected as a bolus (median= 545 MBq, interquartile range = 465-576MBq) through an antecubital venous catheter, and data were acquired for 90 min after injection in 58 frames (18 x 5, 6 x 15 seconds, 10 x 30 seconds, 7 x 1 minute, 4 x 2.5 minutes, and 13 x 5 minutes). For each frame, sono` data were reconstructed using the PROMIS 3D filtered back projection algorithm into a 128 x 128 x 35 image array with a voxel size of 2.34 x 2.34 x 4.25mm^3. Corrections were applied for random coincidences, dead

time, normalization, scatter, attenuation and sensitivity. The dynamic PET images were realigned with statistical parametric mapping (SPM) and averaged. The resultant mean images were co-registered to their corresponding bias-corrected magnetisation-prepared, rapid gradient-echo MRI (MPRAGE) volume. Consistent with previous studies (Hanseeuw et al., 2017; LaPoint et al., 2017) , the geometric transfer matrix (GTM) technique was used to derive partial-volume corrected ROIs. Subsequently, kinetic modelling was performed using the two-stage Multilinear Reference Tissue Model (MRTM2) implemented in PetSurfer (Ichise et al., 2003) to estimate non-displaceable binding potential (BP_{ND}), using the cerebellum as the reference region. Classifications of Aβ "positivity" and "negativity" were assigned based on elevated binding in the striatum, which has been shown to clearly separate the positive and negative groups in our previous work (Annus et al., 2016) as well as others (Handen et al., 2012; Lao et al., 2017).

Statistical analyses

All statistical analyses were performed in MATLAB 2017A and the *R* statistical package. The specific analyses are described below. To determine the *topographical covariance* of Aβ and cortical thickness across the cortex, we first examined correlations between the inter-regional [^{11}C]-PiB BP_{ND} and cortical thickness. To account for the inter-dependency resulting from repeated measurements per participant (i.e. 68 ROIs), mixed effect models were used to examine the relationship

between all brain regions combined across [^{11}C]-PiB BP_{ND} and cortical thickness datasets, treating participants and lobes as random factors. Next, to elucidate the *local associations* of Aβ pathology with cortical thinning, we pursued an unbiased approach and investigated Spearman partial correlations between Aβ binding and cortical thickness within the same ROI while adjusting for age. A Benjamini-Hochberg False Discovery Rate adjusted (FDR) significance level of $p < 0.05$ was used to correct for multiple comparisons.

RESULTS

Demographics and clinical features

Brief demographics of the cohort are shown in Table 1.

Mixed effects modelling of relationship between Aβ and cortical thickness

Across the total sample of DS adults, our mixed effect models indicated a highly significant negative relationship between Aβ binding and cortical thickness [Estimate = -1.2 ± 0.03, t = -39.5], $\chi 2$ (1), $p < 0.001$] (Figure 1A). The statistical significance of this association was retained after we repeated the mixed effect models separately for Aβ+ [Estimate = -0.8 ± 0.04, t = -20.7], $\chi 2$ (1), $p < 0.001$] and Aβ- groups [Estimate = -1.3 ± 0.04, t = -32.9], $\chi 2$ (1), $p < 0.001$] (Figure 1B-C). To further evaluate the consistency of associations across disease stages, we evaluated two

separate mixed effect models for DS adults with no evidence of acquired cognitive impairment, and DS adults judged to have objective cognitive impairment or dementia. While increased Aβ binding was significantly associated with a thinner cortex within each cognitive subgroup, the associations were notably stronger amongst those without acquired cognitive impairment [Estimate = -1.2 ± 0.03, t = -34.0], $p < 0.001$] compared to the group with cognitive impairment or dementia [Estimate = -0.8 ± 0.04, t = -17.0], $p < 0.001$].

Topography of local-to-local associations of Aβ and cortical thickness

Our next objective was to delineate the topography of local Aβ-associated thinner cortices in DS. We investigated Spearman partial correlations between [^{11}C]-PiB BP_{ND} and cortical thickness in the same ROI while adjusting for age and correction for multiple comparisons (FDR), and found widespread extent of highly significant inverse relationships between increased Aβ binding and cortical thickness. The peak correlations were predominantly localized within temporo-parietal ($r \sim -0.4 - -0.7$, $FDR_{adjusted}$ $p < 0.05$). The spatial pattern of Aβ-associated cortical thickness decrease is represented as a heat map on the Desikan-Kiliany template, where the color gradient depicts the strength of the negative correlations (Figure 2). To explore the potential impact of age on these associations, we repeated the analyses without controlling for age, and obtained highly similar distributions of local associations. The 5 ROIs

that did not retain significance were the left entorhinal, left lateral occipital, left lateral orbitofrontal, left paracentral and left pars opercularis cortices.

Associations of Aβ and cortical thinning across levels of amyloidosis and cognitive impairment

Local associations stratified by striatal-Aβ *status*

Next, we inquired whether striatal-Aβ status may modulate the local relationship between Aβ and cortical thickness. A one-way analysis of covariance (ANCOVA), treating the Aβ+ and Aβ- groups as a factor and cortical thickness as a covariate, indicated stronger associations amongst the striatal-Aβ- group in predominantly frontal regions (FDR $_{adjusted}$ $p < 0.05$). These interaction analyses were further corroborated by our within-subgroup correlational analyses, which revealed markedly distinct maps of Aβ-associated cortical thinning in both subgroups (Figure 3). While the striatal-Aβ- group showed significant Aβ-associated cortical thinning in widespread regions involving the frontal and parietal cortices, the peak correlations were mostly restricted to the temporal cortices amongst the striatal-Aβ+ DS adults (FDR $_{adjusted}$ $p < 0.05$). To capture subtle Aβ associations with cortical thinning amongst the striatal-Aβ+ DS adults, we also reported the findings at uncorrected $p < 0.05$ in Supplementary Figure 1, where there was a relatively marked absence of Aβ associations in the frontal lobe.

Local associations stratified by cognitive status

To determine whether Aβ was associated with cortical thickness across varying degrees of acquired cognitive impairment in DS, we repeated these local correlations separately amongst DS adults without acquired cognitive impairment (n = 31) and DS adults with cognitive decline or dementia (n = 13). Within the DS group with no acquired cognitive impairment, we observed a widespread pattern of significant correlations in a pattern that is largely consistent with that of the total sample (FDR $_{adjusted}$ $p < 0.05$). In contrast, correlations between Aβ and cortical thickness did not survive FDR correction, although this was expected considering the smaller sample size (n = 13).

DISCUSSION

In this present study, we mapped the topographic distribution of Aβ binding onto patterns of cortical thickness in DS adults, and present the first evidence that both phenomena are tightly coupled in a spatial pattern consistent with the known "cortical signature" of neurodegeneration in AD. In accordance with our hypothesis, our findings further suggest that the coupling between Aβ and a thinner cortex is more pronounced in the earlier stages of disease, particularly in DS adults with minimal Aβ burden before the onset of acquired cognitive impairment in DS. Collectively, our findings reinforce the notion that early intervention,

particularly with the aim of targeting Aβ, may have the most therapeutic potential during the asymptomatic stages of DS and AD.

While it is well-established that Aβ represents the initiating pathogenic factor in AD, its precise relationships with downstream neurodegeneration and clinical severity have been controversial (Jagust, 2016). Converging data from post-mortem and PET imaging studies have indicated that the regional distribution and severity of Aβ plaques do not correspond with brain atrophy or clinical severity (Chetelat et al., 2010; Erten-Lyons et al., 2013; Josephs et al., 2008). The relevance of the "amyloid cascade" model has also been challenged by the recent spate of failures in Phase III anti-Aβ clinical trials. However, researchers have attempted to reconcile these inconsistencies by citing the disparity between the slow progression of Aβ accumulation and the accelerating trajectories of neurodegeneration (Jack et al., 2013). In this vein, a clearer picture of Aβ-associated atrophy emerges in cohorts that are comprised of cognitively normal elderly and individuals in the early stages of AD (Chetelat et al., 2010; Doré et al., 2013; Jack et al., 2009). For instance, accelerated rates of brain atrophy have been reported in cognitively normal elderly with elevated Aβ burden (Chetelat et al., 2012), consistent with evidence of strong associations between elevated Aβ burden and decreased cortical thickness (Doré et al., 2013). Several aspects of our data therefore are consistent with the notion that the association of Aβ with neurodegeneration is particularly salient during the prodromal stages

of AD in that the coupling of Aβ accumulation with a thinner cortex was stronger in (a) DS adults without acquired cognitive impairment and **(b)** in DS adults who had not reached the threshold to be classified as Aβ+.

After establishing that Aβ accumulation is associated with a thinner cortex in DS, our local correlations sought to delineate the topographical distribution of Aβ-associated atrophy. In the total sample of DS, we found a widespread pattern of negative correlations that peaked within the temporo-parietal cortices, mirroring the "cortical signature" of atrophy in AD (Dickerson et al., 2009). Based on the remarkable spatial overlap between our Aβ-atrophy map and that of the AD "cortical signature", it is conceivable that the topographic distribution of Aβ-associated atrophy may reflect the regional susceptibility to the neurotoxicity of Aβ. Intriguingly, the spatial distribution of our peak correlations is also very similar to that of another study reporting strong associations of Aβ and cortical thinning in healthy controls especially within the bilateral precuneus and medial temporal regions (Doré et al., 2013), both of which have been shown to undergo atrophy in DS adults (Mullins et al., 2013) with elevated burden of Aβ (Annus et al., 2017; Lao et al., 2017).

Another question with important implications for the optimisation of clinical trials is whether the coupling between Aβ and cortical thickness is consistent across varying degrees of disease severity over the course of AD. In keeping with our hypothesis, we observed extensive Aβ-related

atrophy after the correlational analyses were repeated within the subgroup of DS adults who were cognitively stable, suggesting an early process of Aβ-related neurodegeneration preceding the onset of cognitive impairment. This finding was also supported by our interaction analyses which indicated stronger associations amongst the striatal-Aβ-DS, particularly in the frontal cortices. While this could have been attributed to the smaller sample size of the striatal-Aβ+ group, subjecting the correlational tests to a more liberal threshold of uncorrected $p < 0.05$ only yielded a single association in the right pars opercularis (i.e. all other associations in the frontal lobe remained insignificant amongst the striatal-Aβ+ group (Supplementary Figure 1). Relative to the striatal-Aβ- group, the weaker associations within the frontal lobe amongst the striatal-Aβ+ group could be interpreted in light of the known propagation of Aβ (Thal et al., 2014). In other words, DS adults with elevated Aβ burden are most likely further down the pathway to AD, and consequently Aβ accumulation in the frontal lobe may have begun to plateau (Thal et al., 2014). In future longitudinal studies, it would be of clinical interest to examine whether the spatiotemporal trajectories of cortical thinning are distinct in Aβ subgroups.

Despite the prominent correlations observed herein and in other studies (Chetelat et al., 2010; Doré et al., 2013; Jack et al., 2009), the precise mechanisms by which Aβ leads to downstream brain atrophy remains elusive. It has been shown that Aβ oligomers could directly result in

synaptic injury and cell loss (Walsh and Selkoe, 2007). Such a mechanism would entail a spatial correspondence between the presence of early Aβ deposition and neurodegeneration, as evidenced by our findings of prominent local associations in regions typically associated with abundant deposits of Aβ (i.e. frontal and parietal cortices (Arnold et al., 1991; Rowe et al., 2007)).

The coupling of Aβ with cortical thinning in several regions of the medial temporal lobe - despite being a later site of Aβ deposition – also merit further discussion (i.e. fusiform, entorhinal, and inferior temporal cortices amongst others). Given that these regions are amongst the earliest sites of abnormal tau aggregation in the disease course of AD (Braak and Braak, 1991), it is plausible that Aβ-associated atrophy – particularly in the medial temporal cortex where Aβ is not commonly observed in the earlier stages of AD – may be mediated by tau hyperphosphorylation, a phenomenon which may have already begun in our striatal-Aβ+ individuals (Supplementary Figure 1). Moving forward, PET investigations of [^{18}F]-AV1451 for tau and [^{11}C]-PiB imaging in DS cohorts will no doubt clarify this question in future and clarify the relative contributions of tau and Aβ to the disease progression of DS (i.e. The Alzheimer's Biomarkers Consortium – Down Syndrome (ABC-DS) that encompasses the NIAD study; https://niad-project.org/) and the ADDS (Alzheimer's Disease in Downs Syndrome; ; https://www.nia.nih.gov/research/abc-ds).

The widespread prevalence and premature comorbidity of AD pathology in DS presents valuable opportunities to study the early implications of AD pathogenesis within a naturally enriched population. Contrary to the consensus that Aβ is not associated with downstream neurodegeneration in established AD, our present findings in DS showed that the coupling between Aβ deposition and cortical thinning may be more pronounced in the earliest stages of dementia. Furthermore, we showed that Aβ-associated atrophy in DS manifests even in the absence of acquired cognitive impairment or substantial Aβ burden. Moving forward, elucidating the deleterious implications of amyloid-β burden and longitudinal rates of brain atrophy would be of high importance to **(a)** improve our understanding of the underlying neuropathological substrates that drive spatial patterns of downstream neurodegeneration, **(b)** aid development of new disease-modification against AD pathologies, and **(c)** support the utility of amyloid PET imaging to track disease progression and monitor treatment outcomes.

A potential caveat associated with imaging studies of developmental conditions is the uncertainty over Freesurfer's ability to accurately measure cortical thickness due to inherent differences in brain morphology compared to the general population. For instance, reduced signal contrast between the grey and white matter – a phenomenon recently reported in DS (Bletsch et al., 2018) – may hinder reliability of *in vivo* estimates of cortical thickness. While previous studies have used

manual tracing on *a priori* selected brain regions, they were limited by the labour intensive and operator-dependent procedures, both of which are challenges that may hinder their adoption as imaging biomarkers in large scale clinical trials for DS. In addition, only predefined regions may be investigated using a manual tracing approach. Cortical thickness measurements from Freesurfer have also been validated against histological data and other manual measurements (Cardinale et al., 2014; Fischl and Dale, 2000), and has been widely applied to interrogate cortical changes in the DS neuroimaging literature (see Neale et al., 2018 for a systematic review). In future, it will be essential to validate these conclusions using histological data as existing post-mortem studies in DS are scarce.

Finally, ageing presents another caveat in the interpretation of the relationships between Aβ accumulation and cortical thinning. An early process of accelerated age-related cortical thinning has been previously described in DS (Cole et al., 2017), supported by other studies reporting prominent localisation of age-related atrophy in frontal association cortices (Romano et al., 2016; Teipel et al., 2004). In a similar vein, our previous work has shown that the spatial extent of Aβ accumulation increases with age (Annus et al., 2016). In order to guard against the possibility that both Aβ accumulation and cortical thinning are merely progressing along a common age-related pathway, we compared the spatial maps of Aβ-associated atrophy, with and without accounting for

age, and found two largely similar spatial distributions (i.e. Only 5/45 ROIs did not retain statistical significance after correcting for age), supporting the idea that Aβ may exert its deleterious effects on cortical thickness over and above an accelerated ageing process.

Finally, our findings are consistent with a recent case-report of a rare DS patient with partial trisomy of chromosome 21 (PT21) who lacked triplication of APP (Doran et al., 2017). Intriguingly, the patient showed (i) relatively stable cognitive performances over time and had no signs of dementia on neurological examinations; (ii) lower [^{11}C]-PiB binding than healthy controls; (iii) and histological examinations revealed only a single neuritic plaque. Interpreted in light of our strong associations between Aβ and cortical thinning, these findings further argue for an obligatory role of Aβ in driving the AD disease cascade in people with DS. Nevertheless, we cannot be certain as to what extent the proposed role of Aβ in the causation of neurodegeneration and AD in people with DS can be generalised to the typically developing population. However, if such a relationship had not been found in DS, where Aβ levels are markedly increased, that would have been a significant challenge to the amyloid cascade hypothesis. The fact this inverse relationship between Aβ and cortical thickness has been found provides further support for this hypothesis.

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AUTHOR CONTRIBUTIONS

Elijah Mak formulated the research objectives, analyses and wrote the manuscript.

Concepcion Padilla assisted with the interpretation of the results, checking of the analyses and scripts, and provided critical feedback on manuscript.

Tiina Annus, Liam Wilson performed the data collection, clinical / neuropsychological assessments, and provided critical feedback on the manuscript.

Young Hong and Tim Fryer designed the PET data acquisition and image reconstruction protocols, determined SUVRs and binding parametric maps from the PET data, and provided critical feedback on the manuscript.

Jonathan Coles, Franklin Aigbirhio, David Menon, Peter Nestor and Shahid Zaman provided critical feedback on the analyses and manuscript.

Anthony J Holland is principal investigator of the study. He also assisted with the conceptualisation of the study, obtaining funding, supervising data collection, interpretation of the analyses and findings, and provided critical feedback on the analyses and manuscript.

POTENTIAL CONFLICTS OF INTEREST

Nothing to report.

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FIGURE LEGENDS

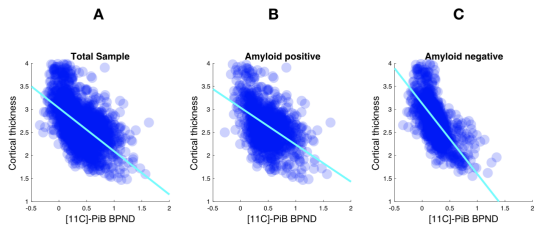
Figure 1. Topographical covariance of Aβ and decreased cortical thickness. The scatter plots depict the associations between Aβ and cortical thickness measures across (a) total sample, (b) DS striatal-Aβ+ adults, and (c) DS striatal-Aβ-adults. Each data point represents a single cortical region of interest from a single subject, parcellated with the Desikan-Killiany template.

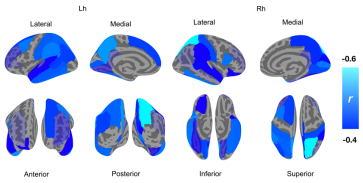
Figure 2. The topographical distribution of local Aβ-associated atrophy in the total sample of DS. These regions showed significantly negative correlations between [^{11}C]-PiB BP_{ND} and cortical thickness (FDR $_{adjusted}$ $p < 0.05$, adjusted for age). The colors represent the strength of the negative correlations, increasing in magnitude from dark blue to cyan. Abbreviations: Lh = Left hemisphere; Rh = Right hemisphere; DS = Down Syndrome.

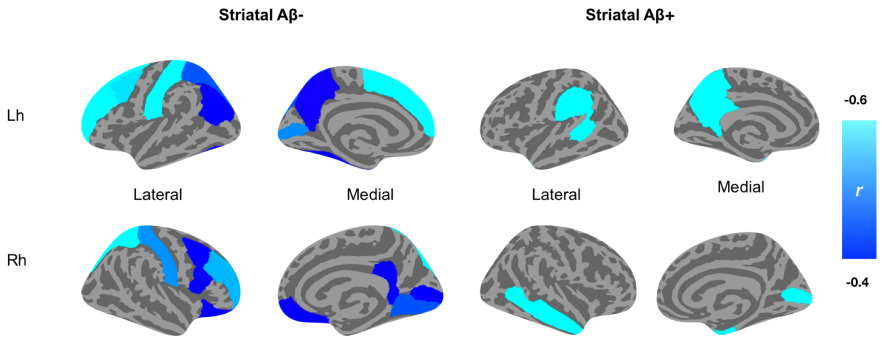
Figure 3. Topographic distributions of Aβ-associated atrophy stratified by Aβ status. Amongst the Aβ- DS adults, local Aβ deposition was significantly associated with decreased cortical thickness in widespread regions predominantly fronto-parietal cortices whereas the spatial extent of associations was more restricted to the temporal cortices and precuneus in the Aβ+ DS adults. Abbreviations: Lh = Left hemisphere; Rh = Right hemisphere; DS = Down Syndrome.

	Adults with Down's Syndrome (n=44)
Age, years (± SD)	41.95 ± 8.7
Female	54.55%
CAMCOG score (± SD)	75.22 ± 19.62
Elevated striatal [^{11}C]-PiB binding (absent/present)	18:26
Acquired cognitive impairment or dementia (%)	30%

Table 1. Brief demographics and cognitive characteristic of the study sample.







HIGHLIGHTS

1. In a sample of adults with Down's Syndrome (DS), amyloid burden (Aβ) was strongly associated with cortical thinning.
2. The topography of Aβ-associated atrophy is similar to the cortical signature of atrophy in Alzheimer's disease.
3. These findings further implicate Aβ in the pathophysiology of DS.
4. Further longitudinal studies are necessary to clarify the extent to which baseline Aβ imaging could predict downstream severity of brain atrophy in DS.